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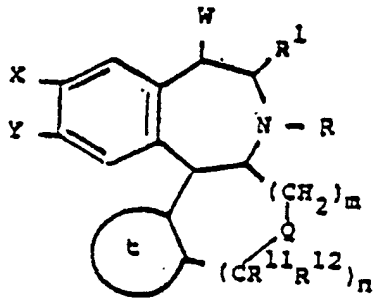
(54) Use of 2,3,4,5-tetrahydro-1H-3-benzazepines in the treatment of neurological disorders.

(57) Methods and compositions are disclosed for treating drug dependence, movement disorder and stereotypic behavior with certain fused benzazepine compounds.



I

EP 0 351 733 A1

METHOD OF TREATING NEUROLOGICAL DISORDERS

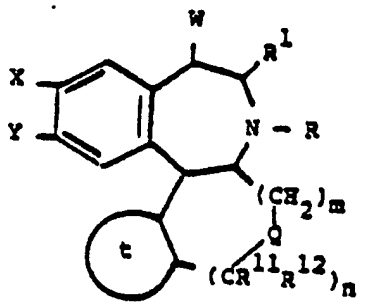
BACKGROUND OF THE INVENTION

This invention relates to the use of certain fused derivatives of compounds having a fused ring nucleus which includes a 2,3,4,5-tetrahydro-1H-3-benzazepine system in the treatment of drug dependence, movement disorders or stereotypic behavior and to pharmaceutical compositions for such purpose.

Substituted 1-phenyl,2,3,4,5-tetrahydro-1H-3-benzazepines have been described in the art. For example, see U.S. Patents 3,393,192, 3,609,138, 4,011,319, 4,284,555 and 4,477,378 as well as British Patent 1,118,688. The compounds employed in the present invention have been described in European published Application Nos. 0 230 270 and 0 299 101. The activities discussed for the compounds disclosed in these patents and applications include anti-bacterial, central nervous system, anti-psychotic, anti-depressive and hypotensive effects.

SUMMARY OF THE INVENTION

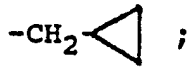
It has now surprisingly been found that the compounds of formula I below or a pharmaceutically acceptable salt thereof can be used in the treatment of drug dependence movement disorders or stereotypic behavior. Such drug dependence includes cocaine or morphine dependence, while the movement disorders and stereotypic behavior include Parkinson's disease, Hunington's chorea, tardive dyskinesias or Lesch-Nyhan disease. The method or use of the invention involves administering to a mammal an effective amount for such purpose of a compound of formula I



I

wherein

R is hydrogen, alkyl, $-CH_2CH=CH_2$ or



;

R^1, R^{11} and R^{12} may be the same or different and each is hydrogen or alkyl;

Q is methylene, -O- or -S-;

m and n are independently variable and may each have a value of 0, 1 or 2, with the provisos that the sum of m and n is not greater than 3, and that m may not equal zero when Q is -O- or -S-;

X is hydrogen, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, hydroxy, alkoxy or trifluoromethyl;

Y is

hydrogen, hydroxy, alkoxy,

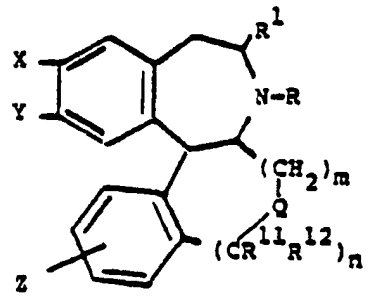
$-O\overset{O}{\overset{\|}{C}}NR^2R^3$, $-O\overset{O}{\overset{\|}{C}}-R^3$, $-NR^1_2$,

-NH C R¹ or -O P (OH)OR¹;
W is hydrogen, hydroxy or alkoxy;

represents a fused thiophene or fused benzene ring, said fused benzene ring optionally being substituted with a substituent Z as defined below;
R^2 and R^3 are independently hydrogen (provided that both are not hydrogen), alkyl, aralkyl, cycloalkyl, aryl, hydroxyalkyl, or alkoxyalkyl;
in addition, when one of R^2 and R^3 is as defined above, the other may be $-R^4NR^5R^6$ {wherein R^4 is alkanediyl, R^5 is hydrogen or alkyl and R^6 is alkyl, or R^5 and R^6 together with the nitrogen atom form a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-(4-alkylpiperazinyl), 4-morpholinyl or 1-(hexahydroazepinyl) group};
in further addition, R^2 and R^3 together with the nitrogen atom may form a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-(4-alkylpiperazinyl), 1-(4-alkoxyalkylpiperazinyl), 1-(4 hydroxyalkylpiperazinyl), 1-(3 hydroxyazetidinyl), 1-(3-alkoxyazetidinyl), 1-(3-hydroxypyrrolidinyl), 1-(3-alkoxypyrrolidinyl), 1-(3- or 4-hydroxypiperidinyl), 1-(3- or 4-alkoxypiperidinyl), 1-(4-oxopiperidinyl) or 1-(3-oxopyrrolidinyl) ring;
in still further addition, when R_2 is hydrogen, R^3 may be $-CHR^7CO_2R^8$, wherein R^7 and R^8 are independently hydrogen, alkyl or aralkyl;
R^9 is alkyl, aralkyl, aryl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, cycloalkylalkyl, alkoxycarbonylalkyl, cycloalkyl, 1-adamantyl, cycloalkoxyalkyl, alkoxy, aralkoxy, cycloalkoxy, aryloxy or $-CHR^7NHR^8$ {wherein R^7 and R^8 are as defined above}; and
Z is X as defined above, amino, alkylamino or

-NH C R¹⁰ {wherein R^{10} is hydrogen, alkyl or aryl}.

A preferred subgenus of compounds of formula I for use in the present invention is represented by structural formula Ia below:



Ia

wherein R, R^1, R^{11}, R^{12}, X, Y, Z, Q, m and n are as defined above.

Y is preferably selected from

-O- C NR^2R^3 (wherein R^8 and R^3 are both alkyl or one of R^2 and R^3 is hydrogen and the other is alkyl), $-NHR^1$ (wherein R^1 is hydrogen or methyl),

-NH C R^1 (wherein R^1 is hydrogen or methyl),

-O C R^9 (wherein R^8 is as defined above) or hydroxy, and more preferably, Y is amino or hydroxy. W is preferably H. X is preferably hydrogen, alkyl, halogen or alkoxy; while Z is preferably hydrogen, halogen, alkyl, hydroxy or alkoxy. R is preferably methyl and R^1 is preferably hydrogen or methyl, more preferably hydrogen. Ring

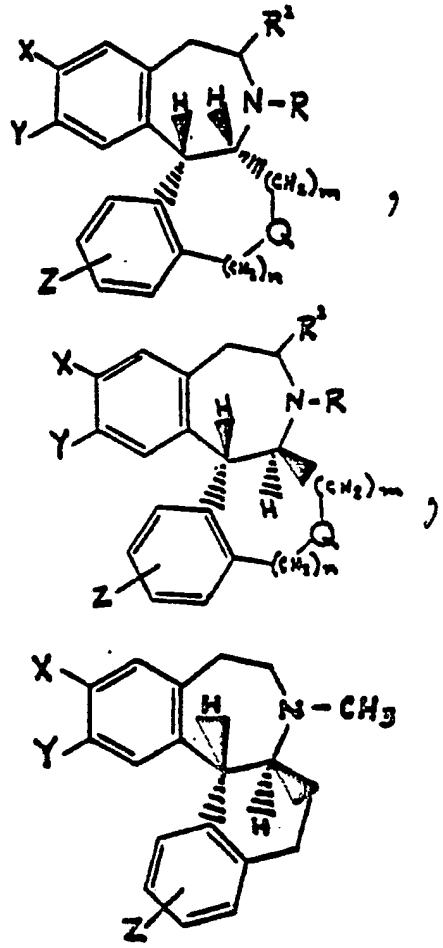
preferably represents a fused benzene ring optionally substituted with halo, alkyl, or -OR^1.

A particularly preferred subgenus of compounds is that of formula Ia above wherein R is methyl; R^1 is hydrogen; Q is methylene; the sum of m and n equals 1; X is hydrogen, methyl, methoxy, chloro or bromo; Y is hydroxy, amino,

-O-C(=O)-R^9 (wherein R^9 is defined as above),

-O-C(=O)-$N(CH_3)_2$ or -$NHCH_3$; and Z is hydrogen, halo, alkyl or -OR^1 (wherein R^1 is hydrogen or alkyl); or a pharmaceutically acceptable salt of such a compound.

The compounds used in the present invention preferably have one of the relative configurations set out below:



wherein R, R^1, Q, m, n, X, Y and Z are as defined above.

Examples of preferred compounds for use in the invention are:

(1) 6,7,7a,8,9,13b-hexahydro-2-hydroxy-3-methoxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(2) 6,7,7a,8,9,13b-hexahydro-2-hydroxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(3) 6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(4) 6,7,7a,8,9,13b-hexahydro-2-hydroxy-3,7-dimethyl-5H-benzo[d]naphtho[2,1-b]azepine;
(5) 6,7,7a,8,9,13b-hexahydro-2-amino-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(6) 6,7,7a,8,9,13b-hexahydro-2-amino-3-chloro-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;

(7) 6,7,7a,8,9,13b-hexahydro-2-amino-3,7-dimethyl-5H-benzo[d]naphtho[2,1-b]azepine;
(8) 6,6a,7,8,9,13b-hexahydro-12-methoxy-7-methyl[1]benzopyrano[4,3-a][3]benzazepine;
(9) 6,6a,7,8,9,13b-hexahydro-7d-methyl[1] benzopyrano[4,3-a][3]benzazepin-12-ol;
(10) 6,6a,7,8,9,13b-hexahydro-3-hydroxy-2methoxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(11) 2-hydroxy-3-methoxy-7-methyl-5,6,7,7a,8, 9,10,14b-octahydro-benzo[d]benzo[3,4]cyclohepta[1,2-b]azepine;
(12) 3-hydroxy-2-methoxy-7-methyl-5,6,7,7a,8, 9,10,14b-octahydro-benzo[d]benzo[3,4]cyclohepta[1,2-b]azepine;
(13) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-3-chloro-7-methyl-benz[d]indeno[2,1-b]azepine;
(14) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-3-methoxy-7-methyl-benz[d]indeno[2,1-b]azepine;
(15) 5,6,7,7a,8,12b-hexahydro 2 amino-3-chloro-7-methyl-benz[d]indeno[2,1-b]azepine;
(16) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-7-methyl-benz[d]indeno[2,1-b]azepine;
(17) 5,6,7,7a,8,12b-hexahydro-3,7-dimethyl-2-hydroxy-benz[d]indeno[2,1-b]azepine;
(18) 5,6,7,7a,8,12b-hexahydro-3-chloro-7-cyclopropylmethyl-2-hydroxy-benz[d]indeno[2,1-b]azepine;
(19) 5,6,7,7a,8,12b-hexahydro-7-allyl-3-chloro-2-hydroxy-benz[d]indeno[2,1-b]azepine;
(20) 5,6,7,7a,8,12b-hexahydro-3-chloro-2-hydroxy-7,8,8-trimethyl-benz[d]indeno[2,1-b]azepine;
(21) 5,6,7,7a,8,11b-hexahydro-3-chloro-7-methyl-thieno[2′,3′:4,5]cyclopenta[1,2-a]-[3]benzazepine-2-ol;
(22) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-3-chloro-benz[d]indeno[2,1-b]azepine;
(23) 6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-5H-benzo[d]naphtho[2,1-b]azepine;
(24) 6,7,7a,8,9,13b-hexahydro-2-amino-3-trifluoromethyl-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
or a pharmaceutically acceptable salt of such compounds.

The invention also involves a pharmaceutical composition suitable for treating drug dependence, movement disorder or stereotypic behavior comprising a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included in the invention is the use of a compound of formula I in the manufacture of a medicament for treating drug dependence, movement disorders or stereotypic behavior.

When utilized herein and in the appended claims, the following terms, unless otherwise specified, have the following scope:

halo - represents fluoro, chloro, bromo or iodo;

alkyl (including, for example, the alkyl portions of alkylthio, alkoxy, aralkyl, alkoxyalkoxy, etc.) - represents straight or branched carbon chains having 1 to 6 carbon atoms;

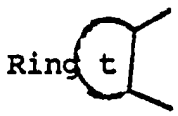
cycloalkyl groups (including the cycloalkyl portion in cycloalkoxy groups) - represents saturated carbocyclic rings having 3 to 7 carbon atoms;

alkanediyl - represents a divalent, straight or branched hydrocarbon chain having from 1 to 6 carbon atoms, the two available bonds being from the same or different carbon atoms thereof, e.g., methylene, ethylene, ethylidene, $-CH_2CH_2CH_2-$, $-CH_2CHCH_3$, $-CHCH_2CH_3$, etc.; and

aryl (including, for example, the aryl moiety in aralkyl or aralkoxy groups) - represents unsubstituted phenyl and phenyl mono substituted by alkyl, hydroxy, alkoxy, halo or trifluoromethyl.

DETAILED DESCRIPTION OF THE INVENTION

The trans form of the compounds of formula I is a preferred embodiment. It is noted that, when R^1 and/or W is other than hydrogen and when R^{11} and R^{12} are different, at least one other assymetric center exists in the compounds of the invention. All such isomeric forms and mixtures thereof are within the scope of the present invention. The isomers may be separated by conventional means such as fractional crystallization or HPLC.



may represent a fused thiophene ring. The sulfur atom in such fused thiophene ring may be in any of the non-fused positions of said ring.

Compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms. In

general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of this invention.

The compounds of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

The compounds of formula I and Ia above as well as the individual compounds (1)-(24) listed above may be prepared by the methods described in European Published Application Nos. 0 230 270 and 0 299 101.

The compounds of formula I possess selective activity for D1 receptors, which is indicative of potential use in treating disorders that may be lessened by D1 antagonists as discussed in Beaulieu, Canadian J. Neur. Sci. 14(3):402 (1987) and Waddington, Gen. Pharmac. 19(1):55 (1988). These disorders include disorders associated with stereotypic behaviors and drug dependence. D1 antagonists have been shown to block cocaine and morphine dependent pleasure sensations making the compounds of the present invention useful in treating drug dependence. Furthermore, although the precise mechanisms involved in a variety of movement disorders are unknown, it is generally accepted that they all use the striatum as a final common pathway. The striatum contains the highest density of D1 receptors suggesting that movement disorders may be treated using D1 antagonists. Consequently, the compounds of formula I have potential utility in treating movement disorders such as Parkinson's disease, Hunington's chorea and tardive dyskinesias. Additionally, D1 antagonists have potential utility as inhibitors of disorders associated with repetitive, stereotypic behavior such as Lesch-Nyhan disease.

For preparing pharmaceutical compositions from the compounds of formula I, inert, pharmaceutically acceptable carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet, the active compound is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets typically contain from 5 to about 70% of the active ingredient dependent upon the potency of the active compound, the size and age of the intended user, and the range of dosage required for the specific therapy. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and other materials typically used in the pharmaceutical industries. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit

dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic aqueous salt solutions, ethanol, glycerine, propylene glycol and the like, as well as mixtures thereof. The solvent utilized will be chosen with regard to the route of administration. For example, liquid preparations containing large amounts of ethanol are not generally suitable for parenteral use.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, lotions and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

A particularly useful dosage form is depot administration, which promotes a prolonged effect of the drug by sustaining the release of the drug. Such depot formulations comprise the formulation of the active ingredient into aqueous suspensions or in oil-based vehicles.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active components. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampules. The unit dosage form can also be a capsule, cachet or tablet itself, or it may be the appropriate number of any of these in a packaged form.

The quantity of active compound in a unit dose preparation may be varied or adjusted from 1 mg to 500 mg, preferably to 100 mg, according to the particular application and the potency of the active ingredient and the intended treatment. This would correspond to a dose of about 0.02 to about 10 mg/kg, preferably to about 2.0 mg/kg, which may be divided over 1 to 3 administrations per day. The composition may, if desired, also contain other therapeutic agents.

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

The following formulations illustrate depot formulations of the invention and may employ any of the compounds of the invention, e.g., (-)-trans-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-7-methyl-5H-benzo-[d]naphtho[2,1-b]azepine:

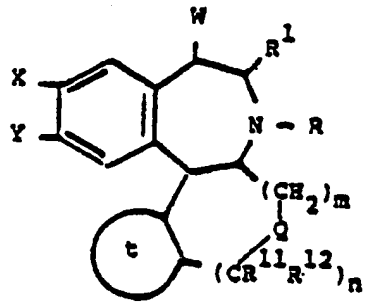
EXAMPLE 1

DEPOT FORMULATIONS			
		mg/g	mg/g
Active Ingredient		300	300
Avicel RC 591		20	--
Benzalkonium Chloride		0.15	--
Edetate Disodium		0.1	--
Methylparaben		--	1.8
Propylparaben		--	0.2
Peanut Oil	to make	--	1 g
Water for Injection	to make	1 g	--

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

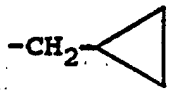
Claims

1. A method for treating drug dependence, movement disorders or stereotypic behavior in a mammal comprising administering an effective amount to said mammal of a compound having the structural formula I or a pharmaceutically acceptable salts thereof,



I

wherein:
R is hydrogen, alkyl, $-CH_2CH=CH_2$ or



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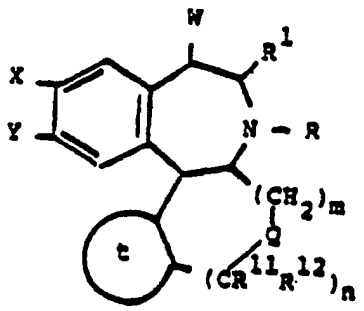
R^1, R^{11} and R^{12} are the same or different and each is hydrogen or alkyl;
Q is methylene, -O- or -S-;
m and n are independently variable and may each have a value of 0, 1 or 2, with the provisos that the sum of m and n is not greater than 3, and that m may not equal zero when Q is -O- or -S-;
X is hydrogen, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, hydroxy, alkoxy or trifluoromethyl;
Y is hydrogen, hydroxy, alkoxy,
$-O\overset{O}{\overset{\|}{C}}NR^2R^3$, $-O\overset{O}{\overset{\|}{C}}-R^9$, $-NR^1_2$, $-NH\overset{O}{\overset{\|}{C}}R^1$ or $-O\overset{O}{\overset{\|}{P}}(OH)OR^1$;
W is hydrogen, hydroxy or alkoxy;
ring t represents a fused thiophene or fused benzene ring said fused benzene ring optionally being substituted with a substituent Z as defined below;
R^2 and R^3 are independently hydrogen (provided that both are not hydrogen), alkyl, aralkyl, cycloalkyl, aryl, hydroxyalkyl, or alkoxyalkyl;
in addition, when one of R^2 and R^3 is as defined above, the other may be $-R^4NR^5R^6$ {wherein R^4 is alkanediyl, R^5 is hydrogen or alkyl and R^6 is alkyl, or R^5 and R^6 together with the nitrogen atom form a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-(4-alkylpiperazinyl), 4-morpholinyl or 1-hexahydroazepinyl group},
in further addition, R^2 and R^3 together with the nitrogen atom may form a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-(4-alkylpiperazinyl), 1-(4-alkoxyalkylpiperazinyl), 1-(4-hydroxyalkylpiperazinyl), 1-(3-hydroxyazetidinyl), 1-(3-alkoxyazetidinyl), 1-(3-hydroxypyrrolidinyl), 1-(3-alkoxypyrrolidinyl), 1-(3- or 4-hydroxypiperidinyl), 1-(3- or 4-alkoxypiperidinyl), 1-(4-oxopiperidinyl) or 1-(3-oxopyrrolidinyl) ring;
in still further addition, when R^2 is hydrogen, R^3 may be $-CHR^7CO_2R^8$, wherein R^7 and R^8 are independently hydrogen, alkyl or aralkyl;
R^9 is alkyl, aralkyl, aryl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, cycloalkylalkyl, alkoxycarbonylalkyl, cycloalkyl, 1-adamantyl, cycloalkoxyalkyl, alkoxy, aralkoxy, cycloalkoxy, aryloxy or $-CHR^7NHR^8$ {wherein R^7 and R^8 are as defined above}; and
Z is X as defined above, amino, alkylamino or
$-NH\overset{O}{\overset{\|}{C}}R^{10}$ {wherein R^{10} is hydrogen, alkyl or aryl}.

2. The use of a compound of formula I below for the manufacture of a medicament for treating drug dependence, movement disorders or stereotypic behavior, wherein the compound has the structural formula



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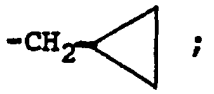
wherein:
R is hydrogen, alkyl, $-CH_2CH=CH_2$ or

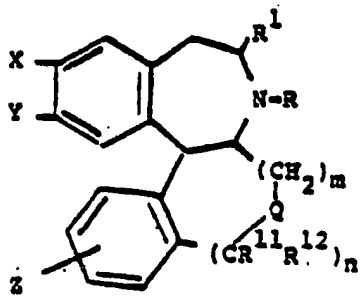


;

R^1, R^{11} and R^{12} are the same or different and each is hydrogen or alkyl;
Q is methylene, -O- or -S-;
m and n are independently variable and may each have a value of 0, 1 or 2, with the provisos that the sum of m and n is not greater than 3, and that m may not equal zero when Q is -O- or -S-;
X is hydrogen, halo, alkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, hydroxy, alkoxy or trifluoromethyl;
Y is hydrogen, hydroxy, alkoxy,
$-O\overset{O}{\overset{\|}{C}}NR^2R^3$, $-O\overset{O}{\overset{\|}{C}}-R^9$, $-NR^1_2$, $-NH\overset{O}{\overset{\|}{C}}R^1$ or $-O\overset{O}{\overset{\|}{P}}(OH)OR^1$;
W is hydrogen, hydroxy or alkoxy;
ring t represents a fused thiophene or fused benzene ring said fused benzene ring optionally being substituted with a substituent Z as defined below;
R^2 and R^3 are independently hydrogen (provided that both are not hydrogen), alkyl, aralkyl, cycloalkyl, aryl, hydroxyalkyl, or alkoxyalkyl;
in addition, when one of R^2 and R^3 is as defined above, the other may be $-R^4NR^5R^6$ {wherein R^4 is alkanediyl, R^5 is hydrogen or alkyl and R^6 is alkyl, or R^5 and R^6 together with the nitrogen atom form a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 1-(4-alkylpiperazinyl), 4-morpholinyl or 1-hexahydroazepinyl group},
in further addition, R^2 and R^3 together with the nitrogen atom may form a 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-(4-alkylpiperazinyl), 1-(4-alkoxyalkylpiperazinyl), 1-(4-hydroxyalkylpiperazinyl), 1-(3-hydroxyazetidinyl), 1-(3-alkoxyazetidinyl), 1-(3-hydroxypyrrolidinyl), 1-(3-alkoxypyrrolidinyl), 1-(3- or 4-hydroxypiperidinyl), 1-(3- or 4-alkoxypiperidinyl), 1-(4-oxopiperidinyl) or 1-(3-oxopyrrolidinyl) ring;
in still further addition, when R^2 is hydrogen, R^3 may be $-CHR^7CO_2R^8$, wherein R^7 and R^8 are independently hydrogen, alkyl or aralkyl;
R^9 is alkyl, aralkyl, aryl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, cycloalkylalkyl, alkoxycarbonylalkyl, cycloalkyl, 1-adamantyl, cycloalkoxyalkyl, alkoxy, aralkoxy, cycloalkoxy, aryloxy or $-CHR^7NHR^8$ {wherein R^7 and R^8 are as defined above}; and
Z is X as defined above, amino, alkylamino or
$-NH\overset{O}{\overset{\|}{C}}R^{10}$ {wherein R^{10} is hydrogen, alkyl or aryl}.

3. The use according to claim 2, characterized in that the drug dependence is cocaine or morphine dependence and the movement disorder or stereotypic behavior is Parkinson's disease, Hunington's chorea, tardive dyskinesias or Lesch-Nyhan disease.

4. The use according to claim 2, characterized in that the compound has the structural formula Ia

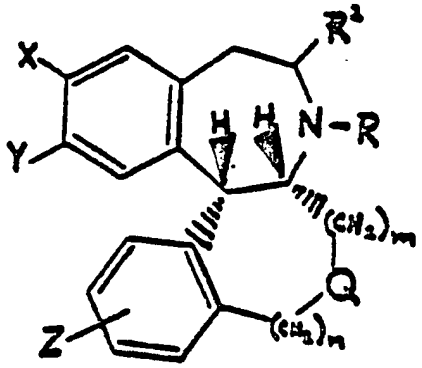


Ia

wherein R, R^1, Q, X, Y, Z, m and n are as defined in claim 2 and R^{11} and R^{12} are both H.

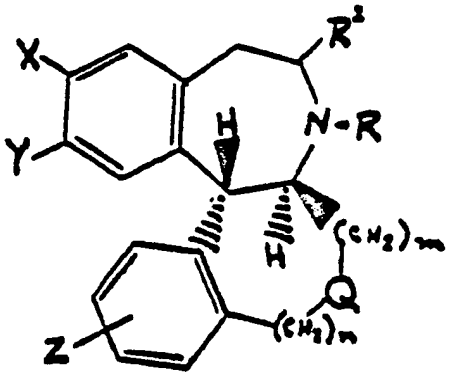
5. The use according to claim 4, characterized in that in the compound of formula Ia:
R is methyl;
R^1 is hydrogen;
Q is methylene;
the sum of m + n equals 1;
X is hydrogen, methyl, methoxy, chloro or bromo;
Y is hydroxy, amino,
-O C R^9, -O C $N(CH_3)_2$ or $-NHCH_3$ {wherein R^9 is as defined in claim 1}; and
Z is hydrogen, halo, alkyl or $-OR^1$ {wherein R^1 is as defined in claim 1}; or pharmaceutically acceptable salts thereof.

6. The use according to claim 2, characterized in that the compound of formula I has the relative configuration:



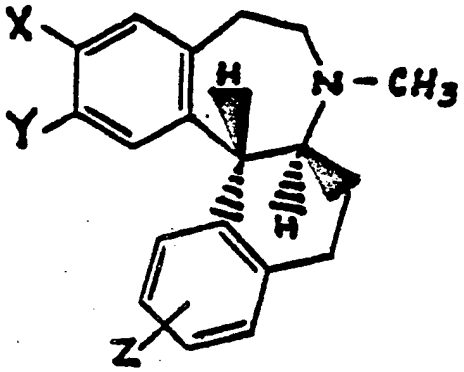
wherein R, R^1, Q, m, n, X, Y and Z are as defined in claim 2.

7. The use according to claim 2, characterized in that the compound of formula I has the relative configuration:



wherein R, R^1, Q, m, n, X, Y, and Z are as defined in claim 2.

8. The use according to claim 5, characterized in that the compound of formula Ia has the relative configuration:



wherein X, Y and Z are as defined in claim 5.

9 The use according to claim 2, characterized in that the compound of formula I is selected from:

(1) 6,7,7a,8,9,13b-hexahydro-2-hydroxy-3-methoxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine; (2) 6,7,7a,8,9,13b-hexahydro-2-hydroxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(3) 6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(4) 6,7,7a,8,9,13b-hexahydro-2-hydroxy-3,7-dimethyl-5H-benzo[d]naphtho[2,1-b]azepine;
(5) 6,7,7a,8,9,13b-hexahydro-2-amino-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(6) 6,7,7a,8,9,13b-hexahydro-2-amino-3-chloro-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(7) 6,7,7a,8,9,13b-hexahydro-2-amino-3,7-dimethyl-5H-benzo[d]naphtho[2,1-b]azepine; or
(8) 6,6a,7,8,9,13b-hexahydro-12-methoxy-7-methyl[1]benzopyrano[4,3-a][3]benzazepine;
(9) 6,6a,7,8,g,13b-hexahydro-7-methyl[1]benzopyrano[4,3-a][3]benzazepin-12-ol;
(10) 6,6a,7,8,9,13b-hexahydro-3-hydroxy-2-methoxy-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine;
(11) 2-hydroxy-3-methoxy-7-methyl-5,6,7,7a,8, 9,10,14b-octahydro-benzo[d]benzo[3,4]cyclohepta[1,2-b]-azepine;
(12) 3-hydroxy-2-methoxy-7-methyl-5,6,7,7a,8, 9,10,14b-octahydro-benzo[d]benzo[3,4]cyclohepta[1,2-b]-azepine;
(13) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-3-chloro-7-methyl-benz[d]indeno[2,1-b]azepine;
(14) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-3-methoxy-7-methyl-benz[d]indeno[2,1-b]azepine;
(15) 5,6,7,7a,8,12b-hexahydro-2-amino-3-chloro-7-methyl-benz[d]indeno[2,1-b]azepine;
(16) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-7-methyl-benz[d]indeno[2,1-b]azepine;
(17) 5,6,7,7a,8,12b-hexahydro-3,7-dimethyl-2-hydroxy-benz[d]indeno[2,1-b]azepine;
(18) 5,6,7,7a,8,12b-hexahydro-3-chloro-7-cyclopropylmethyl-2-hydroxy-benz[d]indeno[2,1-b]azepine;
(19) 5,6,7,7a,8,12b-hexahydro-7-allyl-3-chloro-2-hydroxy-benz[d]indeno[2,1-b]azepine;
(20) 5,6,7,7a,8,12b-hexahydro-3-chloro-2-hydroxy-7,8,8-trimethyl-benz[d]indeno[2,1-b]azepine;
(21) 5.6,7,7a,8,11b-hexahydro-3-chloro-7-methyl-thieno[2',3':4,5]cyclopenta[1,2 a][3]benzazepine-2-ol;
(22) 5,6,7,7a,8,12b-hexahydro-2-hydroxy-3-chloro-benz[d]indeno[2,1-b]azepine;

(23) 6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-5H-benzo[d]naphtho[2,1-b]azepine;
(24) 6,7,7a,8,9,13b-hexahydro-2-amino-3-trifluoromethyl-7-methyl-5H-benzo[d]naphtho[2,1-b]azepine; or
a pharmaceutically acceptable salt of such a compound.

10 The use according to claim 9, characterized in that the compound has a trans configuration.

11. A pharmaceutical composition suitable for treating drug dependence, movement disorders or stereotypic behavior comprising an effective amount of a compound of formula I as defined in claim 2 in combination with a pharmaceutically acceptable carrier.

European Patent Office

DECLARATION

which under Rule 45 of the European Patent Convention shall be considered, for the purpose of subsequent proceedings, as the European search report

Application number
EP 89 11 2959

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of all claims.
Reason:

Claim 1: Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

Claims 1-11: Pharmacological data are lacking from the applicaiton. An indication of the model used for pharmacological testing is also lacking. The fact that the description contains a pharmaceutical formulation of the known compound cannot substitute for the lack of substantiation of the pharmacological activity.
Such pharmaceutical formulations are common practice in pharmacy, and have nothing at all to do with the gist of the invention. In the field of the so called "second medical indication" the essence of the invention is the manufacture of a medicament for a new use. Such new use must then be supported in the description by pharmacological data, or results from pharmacological testing. Indications or suggestions of potential uses clearly represent nothing more than wishful thinking. As a consequence, the claimed pharmacological activity is to be regarded as "paper-pharmacology", the invention is not sufficiently disclosed (EPC Art. 83), and the claims are not supported by the description (EPC Art. 84).
The reference from Can. J. of Neur. Sci. is incorrect.

CLASSIFICATION OF THE APPLICATION (Int. Cl.4)

A 61 K 31/55

Place of search	Date of completion of the search	Examiner
The Hague	19-09-1989	GERLI